sanofi aventis

Because health matters

April 4, 2005

Via fax and UPS

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2005D-004

Draft Guidance for Industry on Nonclinical Safety Evaluation of Drug Combinations

Dear Sir/Madam:

Sanofi-Synthelabo Inc. and Aventis Pharmaceuticals, members of the sanofi-aventis Group, appreciate the opportunity to comment on the above-referenced Draft Guidance entitled "Nonclinical Safety Evaluation of Drug Combinations".

This draft guidance provides recommendations on nonclinical approaches to support the clinical study and approval of fixed-dose combination products, co-packaged products, and adjunctive therapies.

We have evaluated the content of the draft guidance and offer the following comments and/or clarifications for your consideration.

SPECIFIC COMMENTS:

I. INTRODUCTION

Footnote 2: "*... An adjunctive therapy refers to the situation in which a patient is maintained on a second drug product that is used together with (i.e., in adjunct to) the primary treatment, although the relative doses are not fixed and the drugs need not be given at the same time. Adjunctive therapy products may or may not be labeled for concomitant use.*"

The scope of this guidance is considered for fixed-dose combination products, co-packaged products, and adjunctive therapies. It is felt that adjunctive therapy which is not labeled should not be in the scope of this guidance. The prescription of a second drug used together with another treatment is the judgment and responsibility of the prescribing physician. The pharmaceutical manufacturer of a drug cannot take responsibility for any unlabeled adjunct therapy.

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II. NONCLINICAL STUDIES FOR COMBINATION OF TWO (OR MORE) PREVIOUSLY MARKETED DRUGS (FIGURE A)

B. Nonclinical Study Recommendations

Lines 122-126: *"For assessment of general toxicity, a bridging study may be appropriate, provided the duration is sufficient to elicit the toxicity of concern. For example, a general toxicity bridging study of 3 months' duration could be considered for a chronic indication. FDA recommends that combination studies include an assessment of several dose levels of the combination and a high dose of each drug alone."*

We recommend that a harmonized wording be considered since in Part III and IV of the guidance document the toxicity bridging study duration is recommended to be **"up to 90 days".** Additionally, it is unclear why in the general toxicity bridging study for a combination of two (or more) previously marketed drug products a *"high dose of each drug alone"* needs to be tested. The toxicological profile of approved and marketed drug products should normally be known. Therefore, testing of a high dose of each drug alone should only be necessary in exceptional cases.

C. Combinations of Previously Marketed Drug Products: General Procedure

Lines 174-177: *"Combination developmental toxicity studies need not be conducted if one of the drug products is already known to have significant risk for developmental toxicity, because that risk will already be included in the product labeling for the combination."*

We recommend that the agency provide additional guidance on how to proceed if all individually marketed drugs do not have a risk for developmental toxicity. The current text may indicate that in such a case, developmental toxicity studies with the combination are recommended. If so, a recommendation should be provided if one species would be considered sufficient.

III. NONCLINICAL STUDIES FOR A COMBINATION OF DRUGS WHEN ONE OR MORE IS PREVIOUSLY MARKETED AND ONE IS A NEW MOLECULAR ENTITY (FIGURE B)

B. Reproductive and Development Toxicology

Lines 218-221: *"Embryofetal developmental studies of the combination should be conducted unless the marketed drug substance is already known to have significant risk for developmental toxicity. If there is known significant risk, embryofetal developmental studies on the NME would not be needed, because the labeling would not be changed in this regard for the combination."*

We recommend that the agency provide additional guidance in cases where the marketed drug and the NME have shown no risk for developmental toxicity. In such a case, are embryofetal development studies of the combination needed and if so, would one species be considered sufficient.

IV. NONCLINICAL STUDIES FOR A COMBINATION OF TWO OR MORE DRUGS WHEN BOTH ARE NEW MOLCULAR ENTITIES (FIGURE C)

G. Reproductive and Developmental Toxicology

Lines 317-322: *"If developmental toxicity has been assessed only on each NME separately, then FDA recommends that developmental toxicity studies be conducted on the combination as well. Embryofetal developmental studies of the combination may not be needed if one of the NMEs is known from the nonclinical studies to have significant risk for developmental toxicity."*

The current text indicates that embryofetal developmental studies are recommended if the individual NMEs have been tested and no risk for developmental toxicity was observed. Would testing in one species be considered sufficient?

Figure A: Lines 175-177, Box 7: *"Conduct toxicology studies on combination to address concerns."*

Figure B: Lines 392-395, Box 2: *"Usually conduct toxicology study of up to 90 days and embryofetal development study on combination; see text for details on determining whether other studies are appropriate."*

Figure C: Lines 422-425, Box 1: *"Preferably, evaluate each NME (ICH) before evaluating the combination. Usually conduct toxicology study of up to 90 days and embryofetal developmental study on combination (see text for details). If only individual NMEs are studied, use the following approach to address safety concerns."*

We recommend that the agency consider modifying the text to harmonize the study duration and to specify the number of species required for toxicity and embryofetal development studies where applicable. For example:

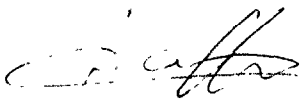
Figure A – Box 7: Conduct toxicology studies on combination to address concerns *(e.g. up to 90 days, 1 species).*

Figure B – Box 2: Usually conduct toxicology study of up to 90 days *in one species* and embryofetal development study *(1 or 2 species?)* on combination; see text for details on determining whether other studies are appropriate.

Figure C – Box 1: Preferably, evaluate each NME (ICH) before evaluating the combination. Usually conduct toxicology study of up to 90 days *in one species* and embryofetal developmental study *(1 or 2 species?)* on combination (see text for details). If only individual NMEs are studied, use the following approach to address safety concerns.

On behalf of the sanofi-aventis Group, we appreciate the opportunity to comment on the *Draft Guidance for Industry on Nonclinical Safety Evaluation of Drug Combinations* and are much obliged for your consideration.

Sincerely,



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